

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

REMARKS

Rejections under 35 U.S.C. 112

The Claimed Invention

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. These differences are used to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. For example, individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to the various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). Other structures derived from Epstein-Barr virus can be used to predict who will develop autoimmune disease. These structures were identified using standard techniques, the known sequences of the Epstein-Barr viral proteins and the known sequences of the autoantigens such as Sm B' and Ro/SSA, and sera from many patients, including a large data base that spanned a number of years in the same patients, allowing the appellants to follow the progression of the disease and markers for the disease, over a period of years. Comparison with normals or individuals who did not develop the disease allow those skilled in the art to identify individuals who are more likely than not to develop autoimmune disease.

The claims are drawn to the following:

Claim 6 has been amended to define a diagnostic assay or test for predicting the risk of developing lupus as including the following reagents:

(1) reagents which can be used to detect in a patient sample materials which are indicative of Epstein-Barr viral infection;

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

- (a) levels of antibodies to Epstein-Barr virus,
- (b) levels of indicators of Epstein-Barr infection of cells, or
- (c) levels of Epstein-Barr DNA or protein in a patient,

wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are peptides of up to forty amino acids in length comprising an amino acid sequence selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPS (SEQ ID NO:26), QKRPSIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGRRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPRRPPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSEDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50) and the peptide consisting of GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), and

- (2) control samples from individuals not at risk of developing lupus, and
- (3) means for determining the differences in the levels of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Support for the amendment to define the specific peptides as consisting of 40 amino acids or fewer and a specific sequence (and SEQ ID NO:98 as only that specific peptide) is found in claim 8 and the specification at page 20, last paragraph.

Claim 7 further defines the reagents of claim 6 for use in particular types of assays: assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

Claim 8 limits the reagents to specific peptides used to detect antibodies, PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPS (SEQ ID NO:26), QKRPSIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRG (SEQ ID NO:99), SGGRG (SEQ ID NO:100), RGGSGRRGRGR (SEQ ID NO:101), RARGRGGRGEKRPRS (SEQ ID NO:102), SSSSGSPRRPPPGR (SEQ ID NO:103), RPPPGRPPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSDDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

Claim 9 limits the assay of claim 8 to a specific peptide which is predictive of an individual not developing lupus, GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Claim 10 defines the assay as useful for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus (in addition to controls who do not have lupus).

Claims 19-22 define methods paralleling the limitations of the diagnostic assay of claims 6-10.

Claim 19 defines a method for determining the likelihood that an individual has lupus induced by Epstein-Barr virus, or is at risk for developing lupus, including the steps of:

- (1) obtaining a sample from the individual to be tested,
- (2) mixing the sample with reagents which can be used to detect levels of
 - (a) antibodies to Epstein-Barr virus,
 - (b) indicators of Epstein-Barr infection of cells, or
 - (c) levels of Epstein-Barr DNA or protein in a patient,
- (3) analyzing the sample, and
- (4) comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing lupus to determine if the differences in levels of the individual and control samples indicates the individual is at a higher risk of developing lupus than controls who are at lower risk of developing lupus.

Claim 20 parallels claim 7. Claims 21 and 22 define the same peptides as claims 8 and 9.

The methods defined by these claims are fully supported by several actual working examples in the specification, showing that the claimed method is predictive of the likelihood one will or will not develop an autoimmune disease such as lupus.

Example 1 is a study to determine which of 233 overlapping octapeptides in an autoantigen, Sm B', are indicative of disease. As shown by Figure 2, all of the anti-Sm sera (i.e.,

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

from patients with lupus) tested bound almost the identical octapeptide structures. As demonstrated by the data in the example, anti-Sm sera binds to PPPGMRPP and structurally similar sequences (Figure 3 SEQ ID NO:4). These sequences included PPPGRRP (SEQ ID NO:1), which is found in the Epstein-Barr Nuclear Antigen-1 (EBNA-1) protein. GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) are also sequences from Epstein-Barr virus Nuclear Antigen-1, but these are similar to a major antigenic epitope of Sm D in lupus patients, GRGRGRGRGRGRGRGRGRGRGGPRRR (SEQ ID NO:9). All three peptides bind at least three times more antibody from the anti-Sm precipitin positive lupus patient sera than the controls. The antibody binding to these peptides in the lupus patient sera was over half of the antibody binding level found for PPPGMRPP (SEQ ID NO:4).

Data was also obtained using a collection of about 80,000 specimens from 26,000 individuals collected and stored over a period of 17 years. This Clinical Immunology database was screened to identify lupus patients who developed anti-Sm under observation. The clinical serum bank was found to contain stored serum specimens from 161 patients with anti-Sm antibodies in at least one serum sample. Four patients were identified among these who, during their SLE clinical course or after initial presentation, converted from being precipitin negative to precipitin positive for antibodies to Sm. Sera from each individual were retrieved from before and after the development of anti-Sm antibodies. For each serum sample, antibody levels were tested by ELISA for binding to Sm and the Sm/nRNP complex. The Ro protein was selected as a control antigen since none of the four patients demonstrated anti-Ro antibodies by Ouchterlony immunodiffusion. Each patient increased binding towards the Sm and Sm/nRNP antigens over time, without an increase in binding to the Ro protein (above background levels) by ELISA. Anti Sm B/B' indicated specificity was confirmed by Western blotting. Binding to Sm B/B'

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

indicated acquisition of a new antibody specificity, since binding to this protein was not detected in the first available sample tested from each patient. Each available serum sample was tested for antibody binding to the 233 overlapping octapeptides of Sm B/B'. Each patient had antibodies which initially targeted the proline rich, repeated motif, PPPGMRP(G)P (SEQ ID NO:4). With time the response diversified to other regions of Sm B/B' when additional serum samples were available.

Sm positive patients from whom a serum sample was available from presentation were also screened. Serum samples from lupus patients stored early in the course of the disease process bind only PPPGMRPP (SEQ ID NO:4) (and neighboring peptides) of the 233 possible octapeptides of B/B', as shown by Figure 4 for one such patient. In addition to the patient presented in Figure 4, two others who initially had a simplified pattern of octapeptide binding were identified. In all three of these cases, only PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) were bound and no other octapeptide were bound. All other anti-Sm positive sera tested bind these octapeptides as well as others. These results are consistent with PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) being the first epitopes of the Sm B/B' autoantigen (Arbuckle, M. R., et al., Scan. J. Immunol. 50:447-55, 1999). This repeated PPPGMRPP (SEQ ID NO:4) motif is an early target in three additional patients tested from whom sera were available from early in their disease. In all of these patients PPPGMRPP (SEQ ID NO:4) is the first autoimmune epitope of the Sm B/B' autoantigen against which one can detect antibody binding.

Four peptide sequences from Epstein-Barr virus were separately evaluated for binding to sera from patients with an autoimmune disease (Figures 3 and 7). All are found in the EBNA-1 (Epstein-Barr virus Nuclear Antigen-1) protein. Subjects with an autoimmune disease, systemic

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

lupus erythematosus, have higher levels of antibodies against PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) than do normal controls. On the other hand the glycine-alanine repeat sequence, GAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), which, after infection by Epstein-Barr virus, is a major epitope in infectious mononucleosis and in normals (Rhodes, G. et al. J. Exp. Med. 165:1026-1040 (1987)) tends not to be bound by patients with lupus (Figure 7). Figure 7 is a graph of the binding to the peptide GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7) from Epstein-Barr virus Nuclear Antigen-1 by lupus sera who all had anti-Sm and anti-nRNP precipitins, as compared to normal control sera. The structures (octapeptides from Epstein-Bar virus nuclear antigen-1) bound by the lupus sera tested is listed in Table 8. These are taken from epitopes with average binding greater than 3 standard deviations about the normal mean (of EBV positive normal controls) and commonly bound by patient sera with an O.D. greater than 0.45 absorbance units. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A U.

Other sequences have also been identified. As described by Example 10, PPPGMRPP (SEQ ID NO:4) constructed on a multiple antigenic peptide (MAP) backbone was coupled to CNBr activated Sepharose™. Each MAP molecule contains eight copies of the PPPGMRPP (SEQ ID NO:4) peptide on a branching polylysine backbone. One ml of sera from a Sm precipitin positive black female lupus patient was passed over the column and extensively washed. Bound antibodies were removed with 3 M guanidine and then dialyzed against 25 mM Tris-HCl pH 8.0. The column affinity purification was repeated using the first round bound material. Purified antibodies were concentrated and quantitated by UV absorption. In order to identify the peptide epitopes recognized by human anti-PPPGMRPP (SEQ ID NO:4) antibodies, a random heptapeptide phage display library from New England Biolabs (Bar Harbor, MA) was

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

screened. A heptapeptide library was selected because all 1.28×10^9 seven amino acid possibilities could be represented (8 a.a. = 2.56×10^{10} combinations, 9 a.a. = 5.12×10^{11} combinations). In this library each random heptapeptide is expressed at the N-terminus of the pIII minor phage coat protein followed by a Gly-Gly-Gly spacer. There is on average five copies of the pIII protein per phage particle. Theoretically, every combination of seven amino acid sequences could be expressed. Antibody-phage complexes were isolated by incubation with protein-A agarose. Following the fourth round of amplification, 70 clones were isolated and sequenced (Table 9). Eleven distinct sequence motifs were identified. Both class I and class II motifs share obvious homology to PPPGMRPP (SEQ ID NO:4) peptide. The binding of anti-PPPGMRPP (SEQ ID NO:4) antibodies to the different types of peptides displayed on the phage was then characterized. Figures 8A-E are graphs of the binding to the overlapping octapeptides from Epstein-Barr virus Nuclear Antigen-1. The binding of three controls are presented in Figures 8A, 8B and 8C and that of two lupus sera in Figures 8D and 8E. Figure 8A is from a normal who has no evidence of having been infected by Epstein-Barr virus by the assay for anti-Epstein-Barr virus Viral Capsid Antigen IgG. The other sera presented (Figures 8B through 8E) are all positive in this assay. The peptides presented had average reactivity at least 3 standard deviations above the normal mean. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A.U. threshold.

In summary, appellants have identified a number of specific peptides that can be used to one can identify patients very early in the disease, based on reactivity with these specific peptides.

Example 9 demonstrates that one can screen for the antibodies using cell line lysates rather than the peptides. Three different cell lines: B95 (marmoset cell line with the most

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

common strain, EBV-1 or -A), Jiyoye cell line (from Burkitt's lymphoma with EBV-2 or -B), and the Ramos cell line which has no EBV infection were obtained. 15 patient and 13 control sera were screened for binding to these different cells lysates. Anti-EBNA-1 is quite obvious as an approximate 70 kD band. All 15 patient sera, as well as 11 of 13 control sera, strongly bind the EBNA-1 protein in both strains. An EBNA-1 monoclonal antibody confirms the identify of this band. Many other proteins are bound by patient and control sera, however there appears to be more patient sera binding to approximately 90 kD, 58 kD, 50 kD, and 36 kD bands.

In summary, the claims define a diagnostic kit and method of use for determining the likelihood that an individual will develop an autoimmune disease. As the examples demonstrate, these assays, and reagents for use therein, have been made, tested, and demonstrated to yield statistically significant results.

The examiner's comment on page 10 of the office action is unjustified. The examples clearly *establish a statistically significant correlation between EBV and lupus. There is no other legal requirement.*

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 6-10 were rejected as indefinite apparent since the examiner thinks there is no function specified by the term "means".

Claim 6 has been amended to more clearly specify that the means are for determining difference in levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in patient and control samples.

As discussed above, there are numerous actual working examples in the application which describe the isolation of antibodies, infected cell lysates, specific peptides, and Epstein-Barr DNA, from patient and control sera, and comparisons thereof, with statistical significance.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Suitable means are also well known to those skilled in the art and indeed are commercially available. The invention resides in the selection of the claimed reagents which are essential for measurement of the levels to be measured, and the understanding of what those measurements can be used to determine: the likelihood someone will develop lupus.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 6-10 and 19-22 were rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. However, since the examiner does not seem to doubt the fact that one skilled in the art can perform the claimed method or make the claimed assay kit, but rather she doubt applicants' scientific conclusions, the legal requirements for written description, utility, and enablement are discussed below.

The legal requirements under 35 U.S.C. 101 and 112 for enablement

An invention must have utility. This requirement can be found in U.S.C. § 101 which states, "Whoever invents or discovers any new and *useful* process or . . . composition of matter . . . may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'l 1987). The *Maas* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

§ 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense," (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.")) (*Brooktree Corp v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron*, 325 F.2d 1389 (CCPA, 1963)).

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Teletronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), citing In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph**, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

Lastly, there is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

The first paragraph of 35 U.S.C. § 112 sets forth the written description requirement for patents as follows:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The standard regarding what is or is not supported by the specification has been clearly articulated as "requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention", i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1117

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

(Fed. Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d 1404, 1405 (CCPA 1971)). Satisfaction of the written description requirement is determined on a case-by-case basis.

The inquiry into whether or not there is an adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. See *In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

In *Amgen v. Hoechst*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003), the Court stated

"The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)."

"Second, "the law makes clear that the specification need teach only one mode of making and using a claimed composition." *Id.* at 160, 57 USPQ2d at 1515 (citing *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998); *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)); see also

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Durel Corp. v. Osram Sylvania Inc., 256 F.3d 1298, 1308, 59 USPQ2d 1238, 1244 (Fed. Cir. 2001)."

The claims comply with 35 U.S.C. 112, first paragraph

There is no requirement under this standard that one prove statistical correlation, however, as discussed above, applicants have done exactly that. The application contains a number of examples that show that one can differentiate between samples of patients with lupus and controls that do not have lupus, both prior to development of symptoms as well as after development of symptoms. These examples demonstrate that specific peptide sequences have been obtained which can be used to screen sera from patients for antibodies which bind to the peptides, some of which are indicative of disease (to a degree that there is 300% more binding from those with or developing disease as compared to negative controls) and some of which are indicative that a patient will not develop disease (the peptide of claims 9 and 22). The examples also demonstrate that assays using cell lysates in functional assays (as defined by claims 7 and 20) can show differences between the two groups, as well as assays for Epstein-Barr DNA. These examples are not hypothetical. They are based on actual patient samples. There are two groups of patients - those being tested after they have developed the symptoms of the disease and those for whom samples are available both before and after development of symptoms. The assay has been shown to be predictive with these samples as well - demonstrating that appellants had in their possession no later than the date of filing of this application, the claimed diagnostic assay and method of use thereof, that they had described the assay and method of use thereof in sufficient detail to enable anyone of skill in the art to make and use the claimed assay and method, and that the method had utility.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Those skilled in the art would have no trouble interpreting the claims. The means portion represents standard assays, although the specific (rather than general) reagents and desired goal are not typical. The test contains reagents reactive with antibodies to EBV antibodies, EBV proteins, or proteins which are known indicators of EBV infection; control samples which are used to eliminate "background" reactions with the reagents not indicative of developing lupus; and means for distinguishing the background reactions (i.e., the reactions between the reagents and the control samples) and the patient samples. If the reaction is greater with the patient sample than with the controls, the patient is at risk. The means are standard - in some cases, the means may be an ELISA assay, where a colored reaction is titrated to quantitate the number of reactants; it may be a chromatographic assay where a spectrophotometer is used to measure the intensity of the reaction; it may be an immunoprecipitation assay; This is certainly a relative analysis, but one commonly practiced by those skilled in the art. Who has not had a blood analysis in which each determination is followed by the normal range, so that one can determine whether one is within the normal range or outside the normal range, and therefore at a great risk?

Claims 6-10 and 19-22 have been rejected apparently for use of the term "likelihood" and "at risk". The terms are well known to those skilled in the art. Particularly in a case such as lupus, where there is a genetic component (same as in some types of cancer or heart disease), there are tests that can be performed to indicate if an individual is more likely than the average individual to develop a disorder, in this case, lupus. Contrary to the examiner's assertion that a cause-and-effect must be established between EBV and lupus before one can claim an assay, this is not the legal standard. The test is whether or not the test yields a more probable than not outcome - which is all many physicians require before initiating far more expensive and comprehensive testing which would be more definitive.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

No more is required under 35 U.S.C. 112, first paragraph. There is no legal requirement to "conclusively" correlate evidence that EBV cause autoimmune disease - the claims are drawn only to an assay and method of predicting the likelihood that a patient will develop the disease. This appellants have shown, using samples obtained from patients and negative controls prior to and after development of disease. Moreover, appellants have described these assays in sufficient detail to enable one skilled in the art, without undue experimentation, to practice the same assays, using the same reagents as claimed. The examiner has provided no evidence to the contrary. All that has been cited in support of the rejection is that the prior art does not establish that the claimed assay and method is useful. This, of course, is not the test under 35 U.S.C. 112.

Moreover, the examiner has completely failed to examine the dependent claims. No rationale is provided for why claims drawn to specific peptides, peptides shown to have reactivity predominantly with patient or control sera, both before and after development of disease, are not in compliance with 35 U.S.C. 112, first paragraph.

In summary, claims 6-10 and 19-22 meet the requirements under 35 U.S.C. 112, first paragraph.

Rejections under 35 U.S.C. 102 and 103

Claims 6, 7, 10, 19, and 20 were rejected under 35 U.S.C. 102(b) as disclosed by Marchini, et al., J. Autoimmunity 7:179-191 (1994) or Petersen, et al., Arthritis and Rheumatism 33(7):993-1000 (1990). Claims 8, 9, 21 and 22 were rejected under 35 U.S.C. 103 as obvious over Petersen, et al. These rejections are respectfully traversed.

Marchini, et al.

Marchini, et al. does not teach that one can predict the likelihood of developing lupus based on an EBV infection. Marchini looks at antibodies in lupus patients and determines

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

whether or not they are reactive with EBV and SmD, an autoantigen. Therefore, Marchini does not teach the method of claim 19 and 20.

Marchini, et al. does not teach a kit as defined by claims 6 and 7, particularly in view of the amendment of claim 6 to incorporate the limitations of claim 8.

Petersen, et al.

Petersen also does not teach that EBV viral infection is predictive of the likelihood of developing lupus. Petersen, et al. only looks at samples *after infection and development of autoimmune disease*, same as Marchini. Therefore, Petersen also does not anticipate claims 19 and 20.

Petersen also does not teach a kit as defined by claims 6 and 7, particularly in view of the amendment of claim 6 to incorporate the limitations of claim 8.

Petersen, et al., also does not make obvious the claimed assay kit and method.

As the examiner correctly notes, Petersen does not teach the claimed peptides, *much less that some are used to indicate the likelihood some will develop lupus and some will not*. Only with experimental data and extensive statistical analysis can one determine that there is a correlation between EBV infection and whether someone develops lupus. The examiner has recognized this as well. With respect to the sequences that the examiner has cited, which is relevant only to the assay claims, these are different from the claimed sequences.

Therefore, the prior art fails to teach the claimed elements, how to modify the sequences to arrive at those claimed by applicants, or any reasonable expectation of success.

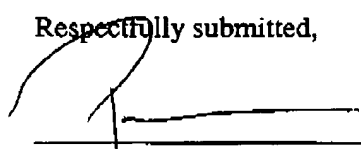
Indeed, Petersen, et al. teaches away from the claimed method because Petersen only looks at patients *after* they have developed the autoimmune disease; applicants claims require testing *prior to development of disease*.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

There is nothing to lead one of ordinary skill in the art to the claimed peptides. It is not enough to say someone would have motivation to look for a reagent: the prior art must lead one skilled in the art to what is claimed, with a reasonable expectation of success. Therefore the claimed reagents cannot be obvious over Petersen.

Based on the foregoing, the compositions of claims 6-10 and methods of claims 19-22 are definite, enabled, comply with the written description requirement, and have utility.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: July 23, 2003
HOLLAND & KNIGHT LLP
2000 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
404-817-8473
404-817-8588 (Fax)

CERTIFICATE OF FACSIMILE TRANSMISSION (37 CFR 1.8a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the Assistant Commissioner for Patents, Washington, D.C. 20231 on the date shown below.

Date: July 23, 2003



Patrea L. Pabst

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